Transient Hyperinsulinaemic Hypoglycaemia in Association with a Novel *ABCC8* Mutation: Expanding the Clinical Phenotypes

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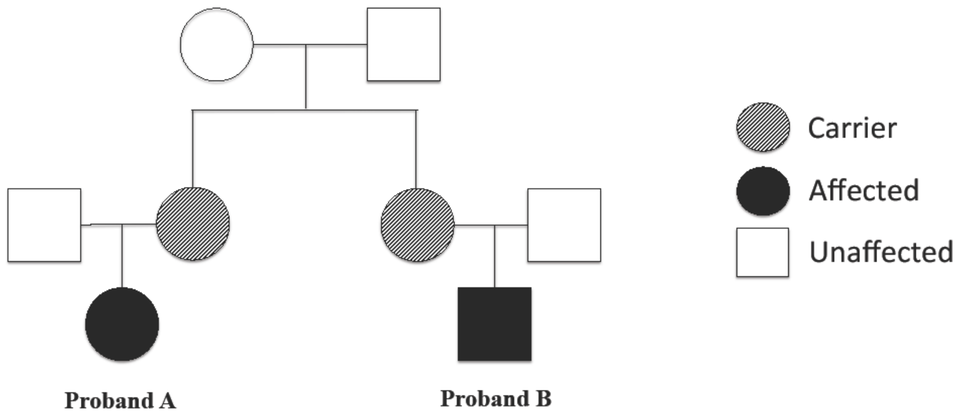
BACKGROUND

- Hyperinsulinaemic hypoglycaemia (HH) results from unregulated insulin secretion from pancreatic β-cells.
- Hyperinsulinaemic hypoglycaemia (HH) can be transient or permanent.
- Transient HH (spontaneous resolution of HH within few weeks) is associated with intrauterine growth restriction, maternal diabetes, erythroblastosis fetalis etc.
- Transient HH has not been reported with *ABCC8/KCNJ11* mutations, which are the commonest cause of HH.

OBJECTIVE

Molecular characterization of a novel *ABCC8* mutation associated with a transient HH phenotype seen in a family with two affected cousins.

PATIENTS

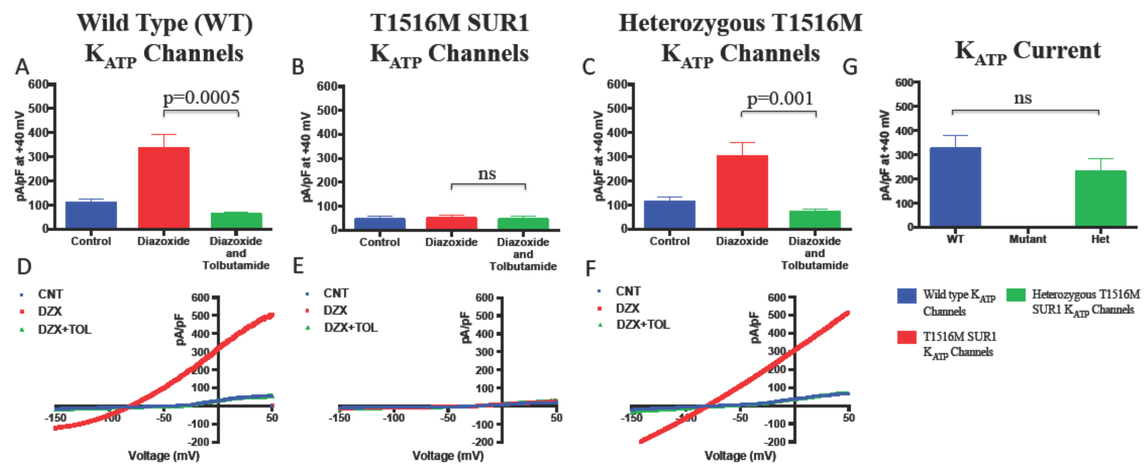


	Proband A	Proband B
Gestational Age (weeks)	40	31
Birth Weight (g)	5370	1815
Age at presentation	1st week	1st week
Hypoglycaemia Screen		
Plasma Glucose (mmol/l)	2.7	0.1
Serum Insulin (mU/l)	<2.0	25.7
C-peptide (pmol/l)	159	-
Serum Cortisol (nmol/l)	433	501
Non-esterified fatty acids (mmol/l)	0.31	<0.05
β-hydroxybutyrate (mmol/l)	<0.05	<0.05
Serum Ammonia (mmol/l)	29	25
Serum Lactate (mmol/l)	1.2	1.6
Plasma Amino acids	Normal	Normal
Urine Organic acids	Normal	Normal
Serum Carnitine profile	Normal	Normal
Maximum glucose infusion requirement (mg/kg/minute)	10	12
Maximum Diazoxide dose required (mg/kg/d)	3	5
Time to resolution of HH (weeks)	12	8
Mutational Analysis *(ABCC8)*	c.4547C>T; p.Thr1516Met	c.4547C>T; p.Thr1516Met

METHODS

- Site-directed mutagenesis was used to create the *ABCC8* point mutation in pcDNA3.1-hamster SUR1 cDNA construct.
- HEK293 cells were transfected with WT/mutant hamster SUR1 cDNA and WT mouse Kir6.2 cDNA using FuGENE.
- Functional properties of channels were studied using whole-cell patch-clamp recordings.
- After attaining whole-cell configuration, cells were voltage-clamped.
- The voltage-clamp protocol consisted of a holding potential of -80 mV, after which the cells were ramped from -150 mV to 50 mV over 1 second (200mV/s) and then stepped back to -80 mV.
- Cells were superfused with 5 K^+ bath solution (CNT), followed by 100 μM DZX to activate K_{ATP} currents, and 100 μM DZX and 100 μM Tolbutamide (DZX+TOL) to inhibit K_{ATP} currents.
- Both homogenous and heterozygous expressions of the mutants were studied.

RESULTS



A, B, C: Graph showing mean pA/pF for Wild type (WT), T1516M SUR1 and Heterozygous T1516M SUR1 K_{ATP} Channels at +40 mV. Data was analyzed using Wilcoxon matched-pairs signed rank test. **D, E, F:** Representative trace from whole-cell patch-clamp recordings for cells expressing WT, T1516M SUR1 and Heterozygous T1516M SUR1 K_{ATP} Channels. **G:** Graph showing K_{ATP} current at +40 mV from HEK293 cells transfected with cDNA of mouse Kir6.2 along with cDNA of WT SUR1, T1516M SUR1 Mutant and 1:1 ratio of WT and T1516M SUR1 Mutant. Data is presented as Mean ± SEM, and was analyzed using Mann-Whitney test, p = 0.28 (not significant [ns]), n = 7-12 cells.

CONCLUSIONS

- This study expands the clinical phenotypes reported with *ABCC8* mutations.
- Molecular characterization was consistent with the observed clinical phenotypes.

The authors have nothing to disclose

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